

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
12 May 2005 (12.05.2005)

PCT

(10) International Publication Number
WO 2005/042726 A3

(51) International Patent Classification⁷: C07K 1/00,
C12N 15/85

(21) International Application Number:
PCT/US2004/036641

(22) International Filing Date:
3 November 2004 (03.11.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/701,401 3 November 2003 (03.11.2003) US

(71) Applicant (for all designated States except US): PRES-
IDENT AND FELLOWS OF HARVARD COLLEGE
[US/US]; 1350 Massachusetts Avenue, Suite 727, Cam-
bridge, MA 02138 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): GLIMCHER, Lau-
rie, H. [US/US]; 51 Hampshire Street, West Newton, MA
02165 (US). OUKKA, Mohamed [US/US]; 46 Englewood
Avenue, Brighton, MA 02146 (US).

(74) Agents: DECONTI, Giulio, A. et al.; Lahive & Cockfield,
I.L.P. 28 State Street, Boston, MA 02109 (US).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

(88) Date of publication of the international search report:
21 July 2005

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: METHODS FOR MODULATING AN IMMUNE RESPONSE BY MODULATING KRC ACTIVITY

(57) Abstract: This invention demonstrates that KRC molecules have multiple important functions as modulating agents in reg-
ulating a wide variety of cellular processes including: inhibiting NFkB transactivation, increasing TNF-alpha induced apoptosis,
inhibiting JNK activation, inhibiting endogenous TNF-alpha expression, promoting immune cell proliferation and immune cell ac-
tivation (e.g., in Th1 cells and/or Th2), activating IL-2 expression e.g., by activating the AP-1 transcription factor, and increasing
actin polymerization. The present invention also demonstrates that KRC interacts with TRAF. Furthermore, the present invention
demonstrates that KRC physically interacts with the c-Jun component of AP-1 to control its degradation. The present invention
also demonstrates that KRC is downstream of several lymphocyte membrane receptors, including TNFR, TCR and TGFβR. Upon
TNFR signaling, KRC associates with the adaptor protein TRAF2 to inhibit NFkB and JNK-dependent gene expression. Upon
TCR stimulation, KRC expression is rapidly induced and KRC physically associates with the c-Jun transcription factor to augment
AP-1 dependent gene transcription. KRC knock-out (KO) T cells have impaired production of AP-1-dependent genes such as CD69
and IL-2. Upon TCR stimulation KRC also associates with the Th2-specific transcription factor GATA3, and T cells lacking KRC
have impaired production of GATA3 dependent Th2 cytokines, IL-4, IL-5 and IL-13. Finally, upon TGFβ receptor signaling, KRC
physically associates with the transcription factor SMAD3 to activate IgA germline transcription in B cells, since KRC KO B cells
have impaired IgA production and germline IgA (GLα) gene transcription. Methods for identifying modulators of KRC activity are
provided. Methods for modulating an immune response and KRC-associated disorders using agents that modulate KRC expression
and/or activity are also provided.



WO 2005/042726 A3